# RESIDENTIAL INDOOR AIR QUALITY GUIDELINE: ACETALDEHYDE

## Background

Acetaldehyde is a colourless, flammable liquid with a pungent and irritating odour, volatile at ambient temperature and pressure, and is found in both indoor and outdoor air. In Environment Canada and Health Canada's 2000 *Priority Substances List Assessment Report: Acetaldehyde*, it was concluded that acetaldehyde is toxic under the *Canadian Environmental Protection Act, 1999* (CEPA) because it may be a genotoxic carcinogen; however, there was considerable uncertainty as to the actual cancer risk. Since the publication of the report, a number of key studies have been published, including those related to the mode of action for acetaldehyde carcinogenesis. Therefore, in order to address the uncertainty in regards to the mode of action of acetaldehyde carcinogenesis, and to more accurately determine the risk to health from levels commonly found in Canadian homes taking into account recently published scientific data, this substance was given high priority for a full health risk assessment and development of a Residential Indoor Air Quality Guideline (RIAQG).

The present document reviews the epidemiological, toxicological, and exposure research on acetaldehyde, as well as the conclusions from a number of comprehensive reviews from internationally recognized health and environmental organizations. The document places an emphasis on research published since the most recent comprehensive review, and proposes new short- and long-term indoor air exposure limits. This RIAQG for acetaldehyde is intended to provide recommended exposure limits which would minimize risks to human health and support the development of actions to limit acetaldehyde emissions. This document also shows that, when compared to the newly proposed guidelines, levels in Canadian houses do not present a health risk.

## Sources and Exposure

Acetaldehyde is found ubiquitously throughout the ambient environment. Natural outdoor sources include higher plant respiration processes and emissions from forest fires. Combustion represents a major anthropogenic source of acetaldehyde, through incomplete combustion of organic material and fuels in motor vehicles. Emissions from industrial production, storage, transport or disposal of products with residual acetaldehyde can also contribute to ambient concentrations. Secondary formation of acetaldehyde can occur through the oxidation of natural and anthropogenic volatile organic compounds (VOCs) present in the atmosphere.

There are numerous sources of acetaldehyde emissions in the indoor environment, often resulting in higher levels compared to outdoors. Incomplete combustion in fireplaces, wood-burning stoves and environmental tobacco smoke, along with certain cooking processes (notably those which use cooking oil), can emit significant quantities of acetaldehyde indoors. Emissions from products for interior finishes (e.g., vinyl flooring and carpets) and wood-based building materials (e.g., fiberboard and particleboard) as well as paints, stains, adhesives, caulking and foam sealants, may also contribute to indoor levels of acetaldehyde. An additional source of acetaldehyde indoors is from the infiltration of vehicle exhaust fumes into the home from an attached garage.

Some consumer products may directly contribute to indoor acetaldehyde levels, such as fragranced consumer products (e.g., air fresheners, liquid fabric softeners, dryer sheets, which may contain acetaldehyde), as well as indirectly via secondary formation of acetaldehyde from indoor reactions of ozone with other organic aerosols. Elevated indoor acetaldehyde levels have been shown to be associated with higher occupant density, likely due to "occupant activities" including, but not limited to, respiration releasing endogenously produced acetaldehyde.

Median acetaldehyde levels from Health Canada exposure studies measured in four cities (Edmonton, Halifax, Regina and Windsor) during winter and summer from 2005 to 2010 ranged from 10.5 to 48.7 $\mu g/m^3$ (indoors) and from 2.4 to 7.2 $\mu g/m^3$ (outdoors) (Health Canada 2010a, 2010b, 2012, 2013). In one study (Windsor), personal exposure measurements were also collected, with a median range of 18.6 to 39.3 $\mu g/m^3$. In these studies, the ratio of indoor to outdoor acetaldehyde concentrations was in general consistently above 2.5, which is indicative of a predominance of indoor sources of acetaldehyde.

## Health Effects

Health effects of exposure to acetaldehyde have been examined in toxicological and controlled human exposure studies, with very little epidemiological evidence related to indoor acetaldehyde exposure. In this assessment, the short-term exposure limit is derived from the results of a controlled human exposure study, whereas the long-term exposure limit is based on toxicological data from a study in a rodent model. Supporting evidence is provided by the results of other toxicological and controlled human exposure studies.

Based on the evidence from human and toxicological studies, the effects of short-term and long-term acetaldehyde inhalation are observed at the site of entry. Key health effects include tissue damage and cancer development, mainly in the upper respiratory tract.

*Human studies*

From the studies with human participants, acute exposure induced eye irritation and potentiated the bronchoconstriction response to methacholine challenge at acetaldehyde concentrations as low as 22 mg/m$^3$, with nose and throat irritation reported at 50–200 ppm (89–357 mg/m$^3$) (Myou et al. 1994b; Silverman, Schulte and First 1946). At higher concentrations (350–1,000 mg/m$^3$), aerosolized acetaldehyde was shown to directly cause bronchoconstriction in people with asthma (Myou et al. 1993,1994b, 1994c, 1995; Fujimura et al. 1997; Prieto et al. 2000; 2002a, 2002b), and a bronchoconstrictive effect was induced in people with allergic rhinitis (2,240 mg/m$^3$) (Prieto, et al. 2002b). Epidemiological data on the long-term effects in humans are limited to a single cross-sectional study of school children (Flamant-Hulin et al. 2010), demonstrating a significant association between acetaldehyde exposure (measured in classrooms) and increased pulmonary inflammation for non-asthmatic children, but not for asthmatic children.

*Toxicological studies*

In laboratory animals, acute acetaldehyde exposure induced irritation and bronchoconstriction responses. For sensory irritation, the lowest concentration that elicited a 50% decrease in respiratory rate was 2,845 ppm (5,080 mg/m$^3$) for a 10–minute exposure in mice (Steinhagen and Barrow 1984), while exposure at ≥ 25 ppm (45 mg/m$^3$) acetaldehyde in rats increased vasodilation in the upper respiratory tract (Stanek et al. 2001).

In animal studies, long-term inhalation exposure to acetaldehyde caused a number of non-neoplastic effects primarily in the upper respiratory tract, specifically inflammation and tissue injury (degeneration, hyperplasia, and metaplasia). In rat studies, long-term acetaldehyde exposure caused adverse effects in the olfactory and respiratory epithelia of the nasal cavity, with lesions noted at exposure concentrations as low as 268 mg/m$^3$, and tissue injury sometimes reported in the larynx, pharynx, and trachea, typically at higher exposure levels (Woutersen et al. 1984, 1986; Saldiva et al. 1985; Appelman et al. 1986; Woutersen and Feron 1987; Cassee et al. 1996; Cassee, Groten and Feron 1996; Oyama et al. 2007; Dorman et al. 2008; Feron, Kruysse and Woutersen 1982). In hamster studies, tracheal and laryngeal tissues were more sensitive than the nasal cavity, although effects were observed at higher concentrations than in the rat studies (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982), indicating a species-related difference. In a small number of animal studies, other adverse effects, namely reduced pulmonary bactericidal activity (Aranyi et al. 1986), increased airway hyperresponsiveness (Kawano et al. 2012), neurological effects (Ortiz, Griffiths and Littleton 1974; Shiohara et al. 1985), and altered gonad weight (Kruysse, Feron and Til 1975) were noted. Growth retardation and mortality were observed at the highest exposure levels (4,464–8,929 mg/m$^3$) (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982).

The International Agency for Research on Cancer (1999) categorized acetaldehyde as a class 2B carcinogen (possibly carcinogenic to humans). Acetaldehyde has been shown to be genotoxic and mutagenic, inducing DNA damage in the form of DNA adducts, DNA–DNA crosslinks, DNA–protein crosslinks as well as more complex adducts (reviewed in Albertini 2013), and mutagenicity in *in vitro* test systems (Environment Canada and Health Canada 2000) as well as in an *in vivo* inhalation study in aldehyde dehydrogenase 2 (ALDH2) knockout mice (Kunugita et al. 2008). Chronic inhalational exposure has caused carcinogenic effects in rats and hamsters at concentrations that induce tissue changes in the upper respiratory tract, with similar specific-related differences in concentrations consistent with the non-neoplastic effects. In rats, chronic exposure resulted in a concentration-dependent increase in adenocarcinoma of the olfactory epithelium and squamous cell carcinoma of the respiratory epithelium occurring at the lowest exposure level (1,339 mg/m$^3$) (Woutersen et al. 1986). In hamsters, chronic exposure at ≥ 2,946 mg/m$^3$ acetaldehyde resulted in a significant increase in tumour

incidence of the larynx (Feron 1979; Feron, Kruysse and Woutersen 1982).

*Susceptible sub-populations*

Studies of short-term exposures in human volunteers provide evidence for asthmatics being a sensitive subgroup to inhaled acetaldehyde (Myou et al. 1993; Prieto et al. 2000, 2002b). An ALDH2 polymorphism (ALDH2-2, the non-functional variant, prevalent in 40 to 50% of the Asian population, which greatly alters the rate of acetaldehyde metabolism following alcohol consumption) may confer additional susceptibility to acetaldehyde exposure. Although an increased severity of acetaldehyde-induced effects has been demonstrated in studies using ALDH2 knockout mice (as compared to wild-type mice) (Isse et al. 2005; Oyama et al. 2007, 2010), in human studies, no significant difference in hyperresponsiveness was observed following inhaled aerosolized acetaldehyde (Teeguarden et al. 2008).

*Mode of Action for Carcinogenesis*

The weight of evidence points to a non-linear (or threshold) mode of action (MOA) for acetaldehyde carcinogenesis. The pattern of genotoxicity and mutagenicity is consistent with a cytotoxic (secondary to a proliferative response), rather than mutagenic (critical early event), MOA for carcinogenicity. Tumour development is proposed to be related to the occurrence of tissue damage and is dependent on saturation of capacity for acetaldehyde metabolism, enhanced cellular proliferation, and mutation in the nasal cavity.

There is evidence that the toxic effects of acetaldehyde may be due, in part, to an overwhelming of the acetaldehyde detoxification capacity at the site of exposure. Evidence indicates that acetaldehyde toxicity is associated with decreased ALDH activity, and is most predominant in ALDH knockout mouse models. In addition, decreased upper respiratory tract uptake of acetaldehyde at elevated concentrations appears to be related to ALDH activity. Following saturation of the metabolic capacity for acetaldehyde, the carcinogenicity of acetaldehyde is proposed to be dependent on the induction of cytotoxicity, leading to increased cell turnover from recurrent tissue damage and repair. While no studies examining the association between acetaldehyde inhalation and cell proliferation in the upper respiratory tract were identified, enhanced cell proliferation of the tongue, epiglottis, and forestomach (i.e. tissues related to route of entry) was observed in a rat study following administration in drinking water (Homann et al. 1997). In addition, acetaldehyde has been shown to induce DNA damage in the form of DNA adducts, DNA-DNA crosslinks, DNA-protein crosslinks as well as more complex adducts. These types of damage, under certain conditions including at high exposure concentrations and in association with tissue damage, lead to mutation.

The pattern of key events leading to tumour development resembles that observed for formaldehyde which is also proposed in the literature to act via a non-linear MOA for carcinogenesis. There is a high degree of similarity in formaldehyde and acetaldehyde carcinogenesis, including similarities in the structure and toxicity of the two compounds, the critical key events including DNA–protein crosslink formation, development of nasal carcinomas in animals at highly irritating and damaging concentrations, and limited evidence of genotoxicity *in vivo*.

## Residential Indoor Air Quality Guideline for Acetaldehyde

The determination of a RIAQG is carried out in two stages. First, a reference concentration (RfC) is derived by applying uncertainty factors to the concentrations at which the most sensitive adverse health endpoint was observed. The RfC approach is used for the determination of a guideline to reduce potential health impacts such as those observed in key toxicological, controlled human exposure, and indoor epidemiological studies.

For the short-term exposure RfC, the exposure period is specified; in the present case, one hour. For the long-term exposure RfC, the exposure is considered to occur over months or years, up to a lifetime.

In the second stage, the short- and long-term exposure RfCs are compared with measured exposures in residential indoor air, and evaluated with respect to their technical feasibility. If the RfC is considered attainable where reasonable control measures are followed, the RIAQG is set equal to the RfC. If the RfC is considered unattainable with currently available risk management technology and practices, the RIAQG may be set at a higher concentration. Setting the RIAQG at a higher concentration than the RfC results in a smaller margin of exposure between the RIAQG and the concentration at which effects have been observed in health studies. Nonetheless, a RIAQG derived in this manner does provide a measure of health protection, while remaining an achievable target for improving indoor air quality when evaluating risk management measures.

*Short-term Residential Indoor Air Quality Guideline*

For short-term exposure to acetaldehyde, in a study investigating bronchoconstriction response in human volunteers, a provocative concentration required to produce a 20% fall in forced expiratory volume in one-second ($FEV_1$) geometric mean for asthmatic subjects of 527 mg/m$^3$ (95% CI: 142–1,149 mg/m$^3$) acetaldehyde following a 2-minute exposure was identified (Prieto et al. 2000). The lower 95% confidence level of 142 mg/m$^3$ was chosen as the point of departure, and uncertainty factors (UFs) of 10 to account for a use of a lowest observed adverse effects level (LOAEL) and 10 to account for additional sensitivity in the human population (e.g., more severe asthmatics, children, ALDH polymorphisms) were applied. Thus, the short-term RfC is 1,420 µg/m$^3$. The Health Canada residential indoor air exposure studies provide a 24–hour integrated sample of acetaldehyde measurements, which does not represent acute or peak exposure. It is evident from these 24–hour measurements that the short-term reference exposure level is significantly higher than the median range of indoor air concentrations. Therefore, as this exposure limit is achievable in Canadian homes, the proposed short-term RIAQG for acetaldehyde is 1,420 µg/m$^3$.

It is recommended that the short-term exposure limit be compared to a one-hour air sample.

*Long-term Residential Indoor Air Quality Guideline*

For chronic exposure, the most sensitive neoplastic endpoint was adenocarcinoma in the nasal cavity of male rats, with the most sensitive non-neoplastic endpoint being degeneration of the olfactory epithelium in rats. As discussed above, a strong body of evidence has also emerged to support the notion that acetaldehyde exerts its carcinogenic effect through a non-linear MOA, with non-neoplastic effects being precursors to a carcinogenic response. Therefore, derivation of an RfC for the neoplastic effects of acetaldehyde is based on the observation of the non-neoplastic effects. A no observed adverse effect level (NOAEL) of 89 mg/m$^3$ is selected, based on degeneration of the olfactory epithelium in rats (Dorman et al. 2008). Using an upper respiratory tract physiologically-based pharmacokinetic model for acetaldehyde inhalation, the human equivalent concentration (HEC) calculated is 120 mg/m$^3$. This value is adjusted for continuous exposure, resulting in an adjusted HEC of 21 mg/m$^3$. Uncertainty factors of 2.5 to account for toxicodynamic differences between animals and humans, 10 for additional sensitivity in the human population, and 3 for uncertainty in the shape of the lower region of the concentration-response curve were applied, resulting in a total UF of 75. Thus, the long-term RfC is 280 µg/m$^3$. The range of median indoor air acetaldehyde concentrations measured in Canadian homes from the Health Canada residential indoor air exposure studies for a 24–hour averaging period was 10.5 to 48.7 µg/m$^3$, with the 95$^{th}$ percentile ranging from 35.6 to149.5 µg/m$^3$. This indicates that Canadian homes would not exceed the RfC of 280 µg/m$^3$. Therefore, the proposed long-term RIAQG for acetaldehyde is 280 µg/m$^3$.

When comparing a measured acetaldehyde concentration with the long-term exposure limit, the sampling time should be at least 24 hours.

## Residential Maximum Exposure Limit for Acetaldehyde

| | Concentration | | |
|---|---|---|---|
| Exposure period | µg/m$^3$ | ppb | Critical Effects |
| Short-term (1 hour) | 1420 | 795 | Increased airway responsiveness in asthmatics |
| Long-term (24 hours) | 280 | 157 | Olfactory epithelial degeneration in the nasal cavity of rats |

Levels of acetaldehyde in a typical Canadian home are likely well below both the short-term and long-term exposure limits, and accordingly are unlikely to pose a health risk.

Strategies for reducing exposure to acetaldehyde include controlling indoor emissions from combustion appliances and smoking. Control measures include the following:

- Not smoking inside the home.
- Properly install and maintain combustion appliances used for heating (e.g., gas and oil furnaces, wood stoves, gas water heaters), with venting outside.
- Use a higher fan setting when cooking on a gas stove, ensure that it vents outside, and preferentially use the back burners.
- When using and applying consumer products such as paints, adhesives, coatings and lubricants, inks, nail polish remover, and fragrances in the home, the area should be well ventilated, and the user should follow all label recommendations. These products should be kept well sealed and/or in non-occupied areas of the

home not connected to the ventilation system, where possible.
- Prevent leaks from an attached garage to the house and make sure that there is an appropriate seal between the home and the garage, particularly for any door that connects the two.
- When performing home renovations, including installation of carpeting or vinyl flooring, and painting in the home, the area should be well-ventilated and the user should follow all label recommendations.

Use of these strategies will help reduce exposure to acetaldehyde and other indoor air contaminants, particularly those in combustion gases and consumer products, including other VOCs.

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